REMARKS

Status of the claims

Claims 8-10 and 16-18 are pending. Claims 8-10 and 16-18 are rejected. Claims 8 and 16 are amended. Claims 1-7 and 12-15 were canceled. New claims 19-22 are added. No new matter is added.

Claim amendment

Claims 8 and 16 are amended to recite that the Type I interferon is ingested upon oral administration to clarify what Applicant considers to be oral administration to overcome rejections under 37 C.F.R. 102(e) & 103(a), as discussed *infra*. Throughout the specification reference is made to interferon being ingested via swallowing with water in human subjects or via feeding via direct delivery to the distal esophagus in mice, e.g., as described in the Brief Description of the Drawings (Figures 11-12 and 20-22) or in Examples 32-35 (pg. 69+).

New claims 19-22 correspond to canceled claims 12-15. Claims 12-15 were canceled previously to overcome a provisional statutory double patenting rejection with copending application

U.S.S.N. 08/946,710 in favor of prosecuting claims 12-15 in the '710 application. Applicants have added new claims 19-22 and canceled corresponding claims 12-15 in U.S.S.N. 08/946,710. No new matter is added in any amended claim or in any new claim.

Objections to the Drawings

Applicant encloses herewith a set of drawings in compliance with 37 C.F.R. 84.

Corrected Combined Declaration and Power of Attorney

Applicant submits herewith a Combined Declaration and Power of Attorney in compliance with 37 C.F.R. 1.63 correctly claiming priority under 35 U.S.C. 120 to prior applications U.S.S.N. 08/631,470, U.S.S.N. 08/408,271 and U.S.S.N. 08/226,631.

The 35 U.S.C. §102(e) rejection

Claims 8-10 and 16-18 are rejected under 35 U.S.C. §102(e) as being anticipated by **Sobel** (U.S. 5,780,021). Applicant respectfully traverses this rejection.

The Examiner states that **Sobel** describes a method of treating or preventing diabetes (col. 1) which inherently would

reduce blood glucose, with Type I interferon using the same dosages (col. 4, ll. 10+; claims 1-2 and 4). The Examiner particularly points Applicant's attention to the description of oral administration (col. 13, ll. 10-30).

Sobel teaches a method of preventing and/or treating autoimmune disorders by administering to a mammal an effective amount of a Type I interferon (col. 1, ll. 46-49). **Sobel** teaches that doses may range from $1x10^5$ to 75×10^6 units, but may be 1×10^4 units or lower (col. 4, ll. 10-17). **Sobel** makes a general statement that the interferon may be administered orally, intravenously, intramuscularly, intraperitoneally, or subcutaneously (col. 4, ll. 24-28).

Applicant notes that claims 8-11 and 16-18 are pending in the instant application. The Examiner's statement as to **Sobel's** teaching that reducing blood glucose is inherent in **Sobel** is directed to canceled claims 12-15. In considering claims 8-10 and 16-18 the Examiner states that **Sobel** teaches a method of treating or preventing diabetes and that **Sobel** describes oral administration.

Applicant's invention, as recited in amended claims 8 and 16 and as discussed *supra*, is drawn to methods of decreasing

the incidence of or onset of insulin-dependent diabetes mellitus in at-risk populations, via ingested interferon, to individuals of an at-risk population. **Sobel** specifically teaches that intraperitoneal delivery of 400,000 units, or a lower dose of 100,000 units, of a hybrid interferon significantly decreased the incidence of and delayed the onset of diabetes in DP-BB rats, as demonstrated by survival curve analysis (col. 9, ll. 59 to col. 2, ll. 42). **Sobel** also teaches what conditions, in an individual or population, may comprise risk factors (col. 10, ll. 60 to col. 11, ll. 3).

Sobel's teachings with regard to what conditions interferon may be used for and the administration of interferon are very general and substantially unsupported. **Sobel** states that interferon generally may be used to treat clinically apparent autoimmune disease, asymptomatic states existing prior to clinically apparent autoimmune and even "pre-states" or "pre-conditions" which exist prior to onset of the symptomatic states (col. 10, ll. 53-58). **Sobel** also teaches a very broad range of dosages of less than 50,000 units to greater than 10 x 10^7 units (col. 4, ll. 15-18). Furthermore, **Sobel** states that the interferon may be administered orally, intraperitoneally, intravenously, intramuscularly, or subcutaneously

(col. 4, ll. 27-28) and in any pharmaceutical composition standard in the art (col. 11, ll. 56 to col. 13, ll. 32).

However, Applicant submits that the examples provided in **Sobel** do not provide an enabling disclosure for oral administration, or even for some types of parenteral administration, of interferon such that a skilled artisan could take the teachings in **Sobel** in combination with his own knowledge of the particular art and be in possession of the invention. A single statement that the interferons may be administered orally is not sufficient for an enabling disclosure. Additionally, given what was known in the art at the time of the instant invention, administration via parenteral injection cannot be equated with oral administration for ingestion.

Sobel's very broad statements notwithstanding, consider that Applicant teaches that in treating experimental allergic neuritis, an animal model applicable to the autoimmune diseases chronic inflammatory demyelinating polyradiculoneuropathy and Guillain-Barré syndrome, using a protocol very similar to **Sobel**, a subcutaneous dose of interferon compared to ingested interferon had no more effect than in untreated animals (pg. 34, ll. 10-24; Fig. 6). Also, in U.S. 5,019,382 cited herein, **Cummins** discloses that interferons have been administered intramuscularly and

intradermally, but seldom intravenously because of substantial adverse effects even from highly purified isolates. Additionally, prior to **Sobel**, **Cummins** taught that parenteral administration of high dose human IFN-alpha caused a flu-like syndrome with significant symptoms in HIV-1 positive patients (**Koech** *et al.* Mol Biother 2:91 (1990); pg. 1 of 5, reference enclosed). Furthermore, at the time of the instant invention, **Cummins** teaches the general knowledge in the art was that interferon, as a protein, would not survive the enzymes in the digestive process (col. 2, ll. 47+) and would not be transported across the gut mucosa (**Lecce** *et al.* J Mol Biotherapy 2:211, pg. 4 of 6 (1990), reference enclosed).

Regardless of the dosage used, **Sobel** simply teaches that for oral administration, interferon may be formulated in any pharmaceutical composition standard in the art, such as used for any other orally administered drug. Optionally, a coating may be applied by any standard means to mask taste or to delay availability to gastrointestinal juices (col. 12, ll. 7-15; col. 13, ll. 11-32). Applicant submits that this is not an enabling disclosure, but rather a generic boilerplate review of packaging as a pharmaceutical composition for any orally administered drug. Regardless of formulation, eventually the interferon would be exposed to the gut

environment. **Sobel** provides no guidance to one of ordinary skill in the art as to how to orally administer the interferons for ingestion to circumvent the problem of enzyme degradation of the interferon in the stomach regardless of the pharmaceutical composition in which it was administered.

It is not a trivial matter to administer drugs, particularly if it has been demonstrated that specific scientific problems need to be overcome for efficacious delivery depending upon the route of administration and that, based on the knowledge at the time, not all routes of administration may be viable to achieve a therapeutic effect. At best, **Sobel** teaches intraperitoneal injection of type I interferon. Given the state of the art, **Sobel** also may provide guidance to one of ordinary skill in the art for intramuscular injections of type I interferons, but does not provide an enabling disclosure for oral administration for ingestion. Thus, given the state of this particular art and what was generally believed about administration of interferon to the gut, one of ordinary skill in the art would not consider a sole statement that interferon may be administered orally as providing sufficient teaching to practice such administration.

Therefore, Applicant submits that in view of the lack of any enabling disclosure for oral administration, i.e., ingestion, of Type I interferon, **Sobel** can not anticipate independent claims 8 and 16. Claims 9-10 and 17-18 depend from independent claims 8 and 16, respectively. These claims further limit the invention as recited in independent claims 8 and 16 with respect to types of interferon and dosage. Applicant submits that, if independent claims 8 and 16 are not anticipated by **Sobel**, then **Sobel** cannot anticipate claims 9-11 and 17-18.

The Examiner has made the statement that reducing blood glucose levels is inherent in the method of **Sobel** because **Sobel** teaches preventing or treating diabetes. Applicant has added new claims 19-22 to correspond to canceled claims 12-15, as discussed *supra*. In the interests of furthering prosecution, Applicant submits that **Sobel** also does not anticipate new claims 19-22, drawn to a method of reducing blood glucose levels via ingested interferon, for the same lack of enabling disclosure for oral administration of interferon to ingest the same in claims 8-11 and 16-18 for the reasons presented *supra*.

For a valid §102 rejection, the prior art references must contain each element of the claimed invention. In view of

Applicant's arguments that **Sobel** does not teach ingestion of interferon, **Sobel** does not teach each element of Applicant's claimed invention. Therefore, as these references are not valid prior art against the instant application under 35 U.S.C. §102 and in view of the preceding amendments and remarks, Applicant respectfully submits that the cited reference does not anticipate claims 8-11 and 16-18 under 35 U.S.C. §102(e). Accordingly, Applicants respectfully request that the rejections of claims 8-11 and 16-18 under 35 U.S.C. §102(e) be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 8-11 and 16-18 are rejected under 35 U.S.C. §103(a) as being obvious over **Sobel** and **Cummins** (U.S. 5,019,382). Applicant respectfully traverses this rejection.

The Examiner states that **Sobel** teaches all the limitations of the claims listed and discussed *supra* with the exception of alternate day dosing. Furthermore, the Examiner states that **Cummins** teaches all the limitations of the claims except the alternate day dosing. **Cummins** does teach a single or multiple daily dose regimen and a staggered regimen of 1-3 days per week or month as an alternative to daily dosing (col. 5, ll. 50-55). With such

flexibility as taught by the reference and that it is common in the art to employ such a regimen instead of continuous dosing, it would have been obvious to one of ordinary skill in the art to adopt an alternate day dosing and administer interferon as shown by **Cummins**. The Examiner also points out that even though **Sobel** teaches the same amounts, the reference further states that the precise amount will depend on the judgement of the attending physician based on considerations of age, weight and condition of the patient.

Sobel and Applicant's invention are as stated *supra*. Applicant's arguments that **Sobel** does not anticipate the instant invention are the same. Also, as the Examiner states, **Sobel** does not teach alternate day administration. Applicant respectfully points out that alternate day dosing is not a limitation recited in any of claims 16-18 cited in this obviousness rejection.

Cummins is cited as providing a motivation for alternate day dosing given the flexibility of dosing regimens in **Cummins** which, although none are alternate day dosing, suggest to one of ordinary skill in the art to use such a regimen in the methods of **Sobel**. Applicant maintains **Sobel** does not anticipate the instant claims 8-10 and 16-18 because an enabling disclosure for oral

administration for ingestion is not provided. Thus, including the limitation of alternate day dosing recited in claim 11 can not render claims 8-10 obvious.

However, the Examiner has stated that **Cummins** does teach all the other limitations of the claims excluding alternate day dosing. Applicant emphatically disagrees with the Examiner's assessment. **Cummins** teaches a method of treating apparent autoimmune disorders characterized by a chronic tissue degenerative inflammatory condition by contacting the interferon with the oropharyngeal mucosa. Such diseases are multiple sclerosis, rheumatoid arthritis and stomatitis in humans and lupus erythematosus in canines (col. 4, ll. 19-33).

Cummins uses the abatement or disappearance of physical symptoms as an indicator of successful treatment of a condition. For example, physical symptoms are the skin lesions in lupus (col. 11, ll. 30-44), the joint pain in rheumatoid arthritis (col. 12, ll. 30-33), the neurologic symptoms in multiple sclerosis (col. 12, ll. 40-45) and the ulcers in stomatitis (col. 13, ll. 59-63). **Cummins** is treating an established disease or condition. Importantly, **Cummins** does not delineate diabetes as one of the species encompassed by the term "apparent autoimmune disorders"

(col. 4, ll. 19-33) and, as the disease must be apparent, certainly can not teach a method of reducing the incidence of or delaying the onset of diabetes in an at risk population.

The Decision by the Board of Patent Appeals notwithstanding, Applicants maintain that **Cummins** does not teach oral administration for ingestion of interferon, as disclosed in the instant specification. Although in its Decision on Appeal for the instant application, the Board defined ingest as "to take or absorb (food) into the body" (The American Heritage College Dictionary, Fourth Ed. Houghton Mifflin co. (2002)), Applicants respectfully submit that the Board did not consider that this definition encompasses all life forms capable of ingestion. Lower life forms may absorb food into the body, however, higher forms of animal life and humans ingest or take food into the body by swallowing. The electronic World Book Dictionary (World Book, Inc. 2001) better defines ingestion as "to take food or other substance into the body for digestion".

Cummins specifically teaches that a dosage of about 0.1 to about 5 IU/lb is administered in a solution or in a novel solid unitary dosage form adapted to be dissolved in saliva when placed in the mouth (Abstract; col. 4, ll. 19-33). As amended, Applicant's

claims 8 and 16 recite oral administration of interferon such that the interferon is ingested. This is not **Cummins's** invention.

Cummins teaches the general knowledge in the art was that interferon, as a protein, would not survive the enzymes in the digestive process and would not be transported across the gut mucosa. To surmount these problems, **Cummins** teaches that it is critical that the interferon is administered in a dosage form adapted to assure maximum contact with the oropharyngeal mucosa of the human or animal (col. 4, ll. 37-41). Applicant has demonstrated in the instant invention that interferon can induce a response when delivered to the stomach and small intestine and interacts with the gut mucosa, such as in a GALT-mediated response (pg. 67, ll. 18 to pg. 68, ll, 19; pg. 74, ll. 19-24).

Although oral administration for the purposes of ingestion, as defined in the instant specification, necessarily requires the interferon initially must be delivered through the oropharynx, the interferon does not remain in the oropharynx for sufficient time to contact and interact effectively with the oral mucosa for uptake and delivery to a systemic location, as taught in **Cummins** (col. 4, ll. 13-18 & 37-41). As disclosed in the instant specification, the interferon effectively bypasses the oropharynx.

When fed to mice, interferon was ingested by delivering it "directly to the distal esophagus, stomach and proximal small intestine **bypassing the oropharynx**" (Applicant's emphasis) (pg. 70, ll. 3-5). Subjects ingested the interferon by taking the drug into the mouth and **immediately swallowing** (Applicants emphasis) with at least 150 mls of water, (pg. 12, ll. 11-16; pg. 15, ll. 13-15). This is not holding the interferon, in any form, in the mouth to contact and absorb into the oral mucosa.

Upon examination of **Cummins** and with the general beliefs and knowledge in the art at that time, one of ordinary skill in the art must conclude that contact of a substance, such as interferon, via the oropharyngeal mucosa is not ingestion. **Cummins** specifically states that his discovery is that interferon was taken up by the oral/pharyngeal mucosa and, as such, one of ordinary skill in the art must ensure that the interferon contacts the oral and/or pharyngeal mucosa (col. 4, ll. 13-18 & 37-41). **Cummins** teaches that in clinical trials patients retained the interferon in the mouth about 15 secs to a minute, depending on the pharmaceutical carrier for the interferon to be absorbed. After sufficient retention in the mouth, the solution was either swallowed

or discharged from the patient's mouth (col. 12, ll. 25-29; Claims 1 and 12).

One of ordinary skill in the art could infer that, as the solution may be spit out, no interferon or a negligible amount was remaining and that swallowing is merely an alternative means of eliminating the saliva and/or remaining solution from the mouth with no benefit provided. This inference is supported by the general belief that interferon would not survive the gastrointestinal environment and further by **Cummins** who hypothesizes that the oral cavities of humans and animals contain receptors for interferon which, when bound, are involved in an immunomodulatory process resulting in a generalized elevation of immunocompetence in the host (**Lecce** *et al.* J Mol Biotherapy 2:211, pg. 5 of 6 (1990)).

Applicant maintains that neither **Sobel** nor **Cummins** teaches oral administration for ingestion of Type I interferons. As such, any motivation for one of ordinary skill in the art to combine alternate day dosing, as suggested in **Cummins**, with **Sobel** is moot because, absent teaching ingestion of Type I interferons in both, not all the elements of the instant invention are present in the combination. For the same reasons **Cummins** can not render claims 8-11 and 16-18 obvious. Furthermore, the combination of

Sobel and **Cummins** cannot remedy the deficiencies in either because **Sobel** and **Cummins** both lack the same element of the invention.

As stated *supra*, claims 9-11 and claims 17-18 depend from independent claims 8 and 16, respectfully. If the combination of **Sobel** and **Cummins** cannot render independent claims 8 and 16 obvious, then neither can the combination render claims 9-11 and claims 17-18 obvious.

Obviousness requires a teaching of all the elements by the prior art with a motivation or suggestion to combine the prior art with a reasonable expectation of success. The combination of **Sobel** and **Cummins** lacks teaching oral administration for ingestion of interferon. Thus, in view of the above claim amendments and remarks, the invention as a whole was not obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicants respectfully request that the rejection of claims 8-11 and 16-18 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed July 31, 2003. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned

attorney of record for immediate resolution. Applicant believes no fees are due, however, if this in error, please debit any fees due from Deposit Account No. 07-1185 on which Applicant's counsel is allowed to draw.

Respectfully submitted,

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